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Novel Approach for the Synthesis of Imidazo and Triazolopyridines from Dithioesters

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Ajjahalli. B. Ramesha,[a#] Nagarakere. C. Sandhya,[b#] Chottanahalli. S. Pavan Kumar,[a] Mahanthawamy Hiremath,[a] Kempegowda Mantelingu[a]* and Kanchugarakoppal. S. Rangappa,[a]*

Abstract: T3P–DMSO mediated desulfurative cyclization of *in situ* generated thioamides serves as an efficient, and versatile method for the synthesis of imidazo[1,5-*a*]pyridines and [1,2,4]-triazolo[4,3-*a*]pyridines with good to excellent yields. Substrates such as 2-methylaminoquinoline and pyrazin-2-ylmethanamine also undergo the corresponding reactions at room temperature. This efficient protocol has several advantages such as mild conditions, short reaction time, operational simplicity and high yields.

Introduction

Imidazo and triazolopyridines, which belong to a class of *N*-bridged 5,6-bicylic heterocycles are important motifs in medicinal chemistry.[1] Imidazo[1,2-*a*]pyridine (Figure 1) is the key structure of anoxiolytic agents (Alpidem),[2a] comprising of drugs used for treatment of insomnia (Zolpidem)[2b] and heart failure (Olprinone).[2c] In addition imidazopyridine derivatives have received considerable attention as core ligands in the field of electronic devices.[3] They have also been identified as calcium channel blockers,[4a] phosphodiesterase 10A (PDE-10A) inhibitors,[4b] and (GABA) modulators.[4c] Furthermore, The triazolopyridine scaffold possess a broad spectrum of biological and pharmaceutical activities,[5a] including antiviral,[5b] antibacterial,[5c] and antidepressent.[5d] Moreover, Pettit *et al*.[6a] reported a unique example of a naturally occurring imidazo[1,5-*a*]isoquinolinedione in the tricyclic structure of cribrostatin **6**, a highly active antimicrobial and antineoplastic agent. Many groups reported the total synthesis of cribostatin analogs.[6b-d]

Early synthetic methods involve the conventional cyclodehydrogenation of amides or thioamides to form cyclic compounds by strong acidic, corrosive reagents such as $POCl_3$,[7a] $SOCl_2$,[7b] etc. Cyclodehydration using Lawesson's reagent[8a] and a modified Mitsunobu reaction[8b] to prepare triazolopyridines have been reported. Riechelt *et al* reported

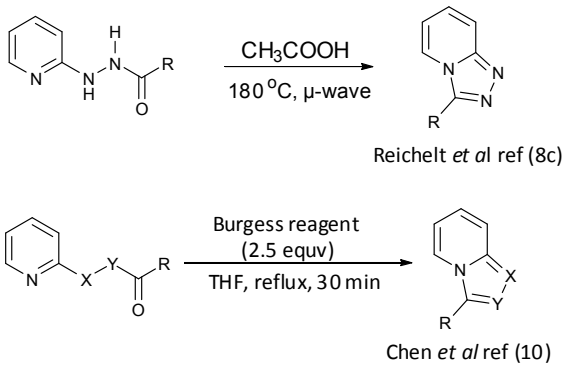

Figure 1 Previous reports

the synthesis of triazolopyridines using dehydrative cyclization in acetic acid under microwave irradiation (figure 1).[8c]

Synthesis of imidazo[1,5-*a*]pyridines by using Tf_2O,[9] and Burges reagent,[10] have been reported. Paoletti *et al* also reported the synthesis of imidazo[1,5-*a*]pyridines starting from carboxylic acids using Propylphosphonic anhydride(T3P).[11] Very recently, Schmidt *et al* synthesized triazolopyridines from 2-hydroxypyridine and imidates using acetic acid.[12] Bhate *et al* synthesized triazolopyridines from hydrazinopyridine and aldehydes.[13] However, the most commonly used procedures have the large excess use of activating reagents, have narrow scope, perform at elevated temperatures, and use multistep synthesis. There is still need for a general procedure applicable for the synthesis of *N*-bridged 5,6-bicyclic pyridines. To address this issue we decided to elaborate a T3P-DMSO mediated cyclodehydration/aromatization strategy under operationally simple and mild conditions applicable to wide variety of substitution patterns. Several groups have reported the utility of T3P reagent.[14a] T3P was initially employed as

[a] *Synthetic Laboratory, DOS in Chemistry, University of Mysore, Manasagangotri, Mysore-570006, Karnataka, India*
[b] *Sharada vilas college, Mysore 570005, Karnataka, India*
* Corresponding authors.
# Authors contributed equally.
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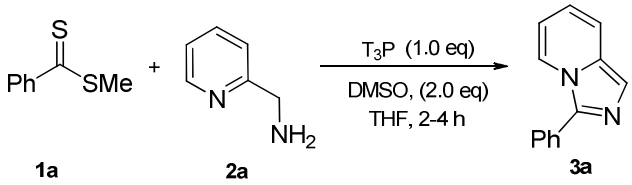
peptide coupling agent,[14b-c] dehydrating agent.[14d–e] Its utility was successfully demonstrated in rearrangement reactions,[14f-g] heterocyclic synthesis[14h-j] and C-C bond formation.[14k] In continuation of our work on synthetic applications of T3P,[15] dithioesters[16] and synthesis of heterocyclic compounds,[17-19] we here in report a new and simple one-pot procedure to access imidazo[1,5-*a*]pyridines and [1,2,4]-triazolo[4,3-*a*]pyridines starting from dithioesters and 2-methylaminopyridines using T3P in THF (50% solution in ethylacetate).

Results and Discussion

We set out to identify the possible mild conditions under which the reaction of 2-methylaminopyridine 2a with phenyl dithioester 1a would proceed. Initially, the reaction of 2- methylaminopyridine **2a** (1.1 eq), T3P (0.5 eq, 50% in EtOAc), DMSO (1.0 eq) in THF at room -temperature for 24 h was carried out. The desired product was obtained in 25% yield (Table 1, entry 1). Upon increasing the amount of T3P to 1.0 eq, yield of the product was increased to 45%

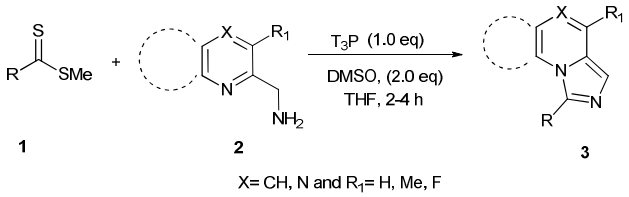


1a **2a** **3a**

Table 1 Optimization of conditions for the synthesis of **3a**

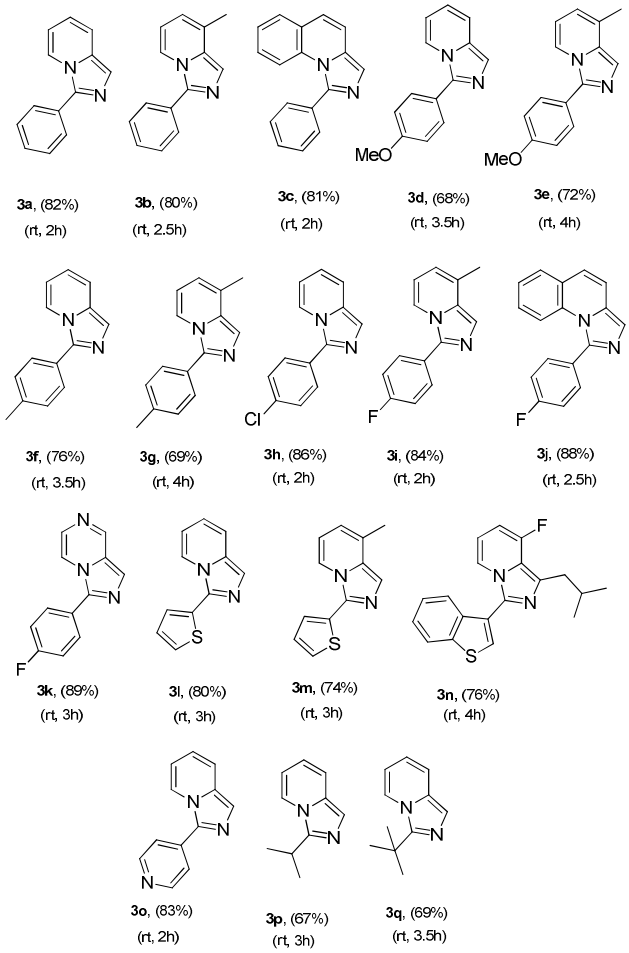
No.	T3P	DMSO	Solvent	Time in h	Temperature	Yield %
1	0.5 eq	1.0 eq	THF	24	RT	25
2	1.0 eq	1.0 eq	THF	24	RT	45
3	1.5 eq	1.0 eq	THF	24	RT	43
4	2.0 eq	1.0 eq	THF	24	RT	42
5	1.0 eq	1.5 eq	THF	12	RT	65
6	1.0 eq	2.0 eq	THF	2	RT	82
7	1.0 eq	2.5 eq	THF	2	RT	78
8	1.0 eq	-	THF	24	RT	-
9	1.0 eq	2.0 eq	THF	2	40 °C	80
10	1.0 eq	2.0 eq	THF	1.5	50 °C	78
11	1.0 eq	2.0 eq	THF	1	60 °C	74
12	1.0 eq	2.0 eq	THF	1	reflux	74
13	1.0 eq	2.0 eq	DMF	2	RT	66
14	1.0 eq	2.0 eq	EtOAc	2	RT	75
15	1.0 eq	2.0 eq	Toluene	2	RT	46
16	1.0 eq	2.0 eq	CH_3CN	2	RT	55
17	1.0 eq	2.0 eq	$CHCl_3$	2	RT	47
18	1.0 eq	2.0eq	Dioxane	2	RT	43

[a]Reactions were performed with T3P (50 % in ethyl acetate) 1.1 mmol of **1a** and 1.0 mmol of **2a**. Yields are isolated yields of chromatographically purified compounds.



X= CH, N and R_1= H, Me, F

Scheme 1 Substrate scope for reaction of amines with dithioesters via cyclodehydration using T3P-DMSO

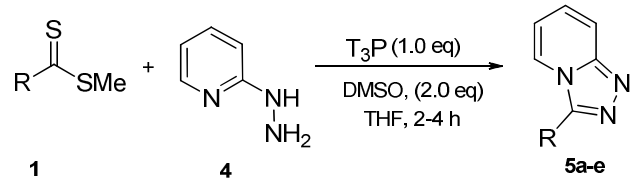


(Table 1, entry-2). No significant improvement in the yield was observed when T3P was increased to 1.5 eq and 2.0 eq (Table 1, entries 3-4). Further, the effect of DMSO was also investigated (Table 1, entries 5-7). Significant improvement in the yield of **3a** was observed when the amount of DMSO was increased (Table 1, entries 5-6). No significant change in the yield was observed when DMSO was increased to 2.5 eq (Table 1, entry 7). We found that with 2 methylaminopyridine (1.1 eq), dithioester (1.0 eq), T3P (1.0 eq), and DMSO (2.0 eq), the reaction condition was ideal. The reaction did not take place at room temperature for 24 h in the absence of DMSO and this made the point obvious that DMSO was needed

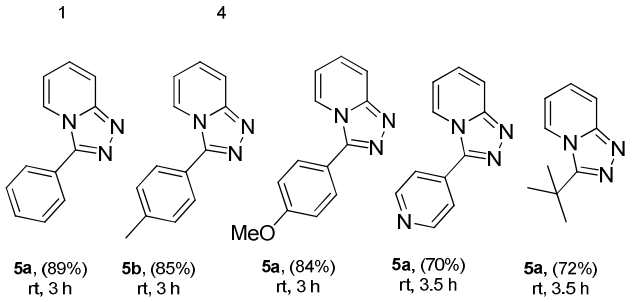
. Effect of the temperature was also tested, as the temperature increase no significant improvement in the yield was observed (Table 1, entries 9-12). The solvents screened included THF, DMF, EtOAc, toluene, CH_3CN, $CHCl_3$, and dioxane, among which THF was found to be the preferred solvent (Table 1, entries 6, 13-17).

Reactions of 2-methylaminopyridine with a range of dithioesters were evaluated under optimized conditions (Scheme 2). In all cases, products were obtained in good yields at room temperature. The presence of electron withdrawing and electron donating substituents on the aromatic rings of the dithioesters did not affect the efficiency of reaction. Dithioesters bearing halogens such as –F, –Cl was employed and the desired products were obtained in excellent yields. The hetero-cyclic dithioesters like thiophene (**3l** and **3m**) benzothiophene (**3n**) and pyridine (**3o**) were compatible in this reaction to give the desired products without polymerization. The reaction was successfully carried out with various aliphatic dithioesters like isopropyl (**3p**) and isobutyl (**3q**). Importantly other amines including 2-methylaminoquinoline and pyrazin-2-ylmethanamine (**3j** and **3k**) also underwent the reaction under equally mild conditions (scheme 1).

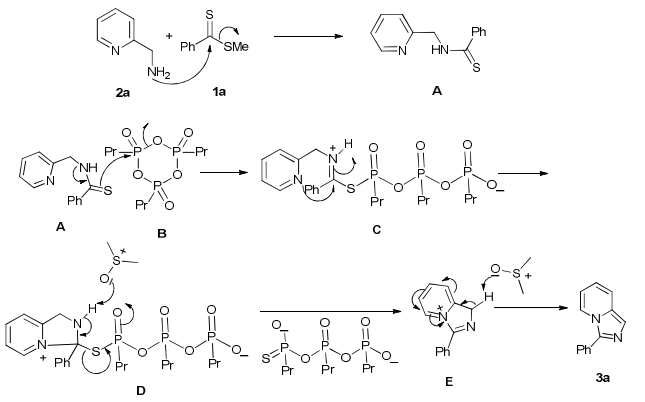
The scope of the reaction was further enhanced with the different amine substrate like 2-hydrazinylpyridine. Surprisingly, all reactions took place at room temperature (scheme 2).



Scheme 2 Substrate scope for reaction of 2-hydrazinylpyridine with dithioesters via cyclodehydration using T3P-DMSO



A plausible mechanism for the cyclization reaction leading to imidazo[1,5-*a*]pyridine is displayed in Scheme 3. In the reaction, 2-methylaminopyridine **2a** reacts with phenyl dithioester **1a** to give *N*-2-pyridylmethyl thioamide **A**. Thioamide **A** reacts with T3P[20-21] to give an intermediate **C**, which undergoes intramolecular cyclization to give cyclic compound **D**. Deprotonation of the cyclic product **D** by DMSO gives **E**, which on further deprotonation generates the final product **3a**.



Scheme 3 Plausible mechanism for the formation of imidazo [1,5-*a*]pyridine

Conclusion

In conclusion, a mild, an efficient substitution and intramolecular cyclization of the pyridine 2-methylamine and dithioester leading to imidazo[1,5-*a*]pyridines and [1,2,4]-triazolo[4,3-*a*]pyridines have been developed. The transformation affords the products under mild conditions in good to excellent yields at room temperature. The key step is intramolecular cyclization of *in situ* generated thioamides. The overall process is facilitated by the combined action of T3P and DMSO.

Experimental section:

(3a): 3-phenylimidazo[1,5-*a*]pyridine

Pale yellow solid (164mg, 82%); MP 101–103 ^{o}C; ^{1}H NMR (400 MHz DMSO-d_6): δ 6.70–6.66 (m, 1H), 6.82–6.79 (m, 1H), 7.45 (t, J = 7.2 Hz,1H), 7.54–7.50 (m, 3H), 7.62 (d, J = 8.8 Hz, 1H), 7.81–7.79 (m, 2H), 8.42 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 137.7, 131.8, 130.6, 128.5, 128.1, 127.8, 122.4, 122.1, 121.4, 119.1, 118.9, 113.9, 113.8; HRMS (ESI-MS): m/z [M+H]$^+$ Calcd for $C_{13}H_{10}N_2$: 195.2319 found: 195.2321.

(3b): 8-methyl-3-phenylimidazo[1,5-*a*]pyrazine

Pale yellow solid; yield: 160mg (80%); MP 85–87 ^{o}C; ^{1}H NMR (400 MHz DMSO-d_6): δ 8.32 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 7.6 Hz, 2H), 7.54–7.47 (m, 3H), 7.40 (d, J = 7.2 Hz, 1H), 6.69 (t, J = 6.8 Hz, 1H), 6.60 (t, J = 7.2 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 135.9, 130.6, 129.3, 128.6, 128.4, 128.2, 127.7, 121.9, 118.5, 117.8, 113.6, 12.8; HRMS (ESI-MS) m/z: Calcd for $C_{14}H_{12}N_2$ [M + H]$^+$ 209.2585 found: 209.2574.

1-phenylimidazo[1,5-*a*]quinoline (3c)

Yellow solid; yield: 162mg (81%); MP 102–104 ^{o}C; ^{1}H NMR (400 MHz DMSO-d_6): δ 7.78–7.76 (m, 1H), 7.60–7.53 (m, 6H), 7.51 (d, J = 9.2 Hz, 1H), 7.37–7.33 (m, 2H), 7.25–7.20 (m, 1H), 7.19 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 142.0, 134.1, 132.0, 130.5, 129.8, 129.8,

129.3, 129.2, 127.9, 125.7, 125.6, 122.74, 122.70, 121.7, 117.6; HRMS (ESI-MS) m/z: Calcd for $C_{17}H_{12}N_2$ $[M + H]^+$ 245.2906 found: 245.2907.

(3d): 3-(4-methoxyphenyl)imidazo[1,5-*a*]pyridine

Brown solid; yield: 136mg **(**68%); MP 122–124 °C; ^{1}H NMR (400 MHz DMSO-d_6): δ 9.08 (d, *J* = 0.8 Hz, 1H), 8.32 (d, *J* = 5.2 Hz, 1H), 7.94 (s, 1H),), 7.83 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 5.2 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.3, 146.8, 139.2, 129.7, 129.2, 127.4, 125.4, 121.8, 115.1, 114.9, 55.8; HRMS (ESI-MS) m/z: Calcd for $C_{14}H_{12}N_2O$ $[M + H]^+$ 225.2579 found: 225.2576.

(3e): **3-(4-methoxyphenyl)-8-methylimidazo[1,5-*a*]pyridine**

Oily Compound; yield: 144mg (72%); ^{1}H NMR (400 MHz DMSO-d_6) δ 8.16 (d, *J* = 6.0 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.48 (s, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.56–6.59 (m, 2H), 3.79 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.8, 138.3, 132.4, 17.6, 129.7, 128.2, 122.8, 119.9, 119.1, 119.0, 118.4, 118.2, 114.7, 55.7; HRMS (ESI-MS) m/z: Calcd for $C_{15}H_{14}N_2O[M + H]^+$ 239.2845 found: 239.2847.

(3f): 3-(*p*-tolyl)imidazo[1,5-*a*]pyridine

Pale green solid; yield: 138mg (69%); MP 90–92 °C; ^{1}H NMR (400MHz DMSO-d_6): δ 8.20 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.52 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 2H), 6.69–6.65 (m, 1H), 6.53–6.49 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.6, 132.6, 131.3, 129.7, 129.5, 127.9, 127.7, 127.3, 121.43, 121.41. 120.1, 119.3, 119.2, 118.9, 113.0, 112.9, 21.4; HRMS (ESI-MS) m/z: Calcd for $C_{14}H_{12}N_2$ $[M + H]^+$ 209.2585 found: 209.2587.

(3g):8-methyl-3-(p-tolyl)imidazo[1,5-*a*]pyridine

Pale yellow solid (140mg, 70%); MP 90–92 °C; ^{1}H NMR (400M Hz DMSO-d_6): *δ* 2.30 (s, 3H), 2.32 (s, 3H), 6.38–6.37 (m, 2H), 7.21 (d, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 0.8 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 8.00–7.98 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 138.7, 138.6, 132.6, 129.7, 129.5, 128.6, 128.0, 127.8, 127.4, 119.3, 119.2, 118.9, 118.7, 117.7, 117.6, 117.5, 113.3, 113.2, 113.1, 21.4, 17.8; HRMS (ESI-MS): m/z $[M+H]^+$ Calcd for $C_{15}H_{14}N_2$: 222.2851 found: 222.2864.

(3h): 3-(4-chlorophenyl)imidazo[1,5-*a*]pyridine

Pale yellow solid; yield: 172mg (86%); MP 105–107 °C; ^{1}H NMR (400MHz DMSO-d_6): δ 8.35–8.33 (m, 1H), 7.78–7.74 (m, 2H), 7.60–7.57 (m, 1H), 7.54–7.49 (m, 3H), 6.83–6.78 (m, 1H), 6.71–6.67 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 136.4, 133.4, 132.0, 129.5, 129.4, 128.9, 122.0, 120.8, 120.1, 118.9, 114.3; HRMS (ESI-MS) m/z: Calcd for $C_{13}H_9ClN_2$ $[M + H]^+$ 229.6770 found: 229.6774.

(3i): 3-(4-Fluorophenyl)-8-methylimidazo[1,5-*a*]pyridine

Oily compound (168mg, 84%); ^{1}H NMR (400 MHz DMSO-d_6): *δ* 8.23–8.21 (m, 1H), 7.84–7.80 (m, 2H), 7.51 (s, 1H), 7.36–7.31 (m, 2H), 6.60 (d, *J* = 5.6 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 163.3, 161.1, 137.9, 132.8, 130.3, 130.2, 128.2, 127.3, 127.2, 119.9, 119.76, 119.71, 118.3, 116.4, 116.2, 114.0, 17.6; HRMS (ESI-MS) m/z: Calcd for $C_{14}H_{11}FN_2$ $[M + H]^+$ 227.2489 found: 227.2488.

(3j): 1-(4-fiurophenyl)imidazo[1,5-*a*]quinoline

Oily Compound (176mg, 88%); ^{1}H NMR (400 MHz DMSO-d_6): *δ* 7.77 (d, *J* = 7.6 Hz, 1H), 7.66–7.62 (m, 2H), 7.53 (s, 1H), 7.50 (d, *J* = 9.6 Hz, 1H), 7.41 (m, 5H), 7.19 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 164.0, 161.6, 146.9, 143.7, 143.6, 143.5, 138.0, 130.7, 130.6, 130.5, 129.4, 127.6, 126.6, 126.0, 125.6, 116.6, 116.4; HRMS (ESI-MS) m/z: Calcd for $C_{17}H_{11}FN_2$ $[M + H]^+$ 263.2810 found: 263.2818.

(3k): 3-(4-fiurophenyl)imidazo[1,5-*a*]pyrazine

Oily Compound; yield: 178mg (89%); ^{1}H NMR (400 MHz DMSO-d_6): δ 9.12 (s, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 7.98–7.92 (m, 3H), 7.58 (d, *J* = 5.2 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 161.6, 146.9, 149.7, 143.7, 143.6, 138.3, 130.7, 130.5, 129.4, 127.6, 126.6, 126.0, 125.6, 116.6, 116.4; HRMS (ESI-MS) m/z: Calcd for $C_{12}H_8FN_3$ $[M + H]^+$ 213.2104 found: 213.2102.

(3l): 3-(thiophen-3-yl)imidazo[1,5-*a*]pyridine

Pale brown solid (160mg, 80%); MP 106–108 °C; ^{1}H NMR (400 MHz DMSO-d_6): *δ* 8.49 (d, *J* = 6.4 Hz, 1H), 7.66– 7.58 (m, 3H), 7.50 (s, 1H), 7.19–7.17 (m, 1H), 6.82–6.74 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 133.1, 132.7, 131.9, 128.5, 126.7, 126.6, 124.28, 124.23, 122.6, 121.08, 121.03, 119.6, 118.9, 114.5; HRMS (ESI-MS) m/z: Calcd for $C_{11}H_8N_2S$ $[M + H]^+$ 201.2596 found: 201.2593.

(3m): 8-methyl-3-(thiophen-2-yl)imidazo[1,5-*a*]pyridine

Pale yellow solid; yield: 148mg (74%); MP 110–112 °C; ^{1}H NMR (400 MHz DMSO-d_6): δ 8.39 (d, *J* = 6.8 Hz, 1H), 7.67 (d, *J* = 3.2 Hz, 1H), 7.61 (d, *J* = 4.8 Hz, 1H), 7.50 (s, 1H), 7.20 (t, *J* = 4.0 Hz, 1H), 6.74 (t, *J* = 6.8 Hz, 1H), 6.63 (d, *J* = 6.4 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 133.3, 133.2, 132.9, 128.5, 128.7, 126.7, 124.3, 124.2, 120.5, 120.0, 119.9, 118.5, 114.6, 17.6; HRMS (ESI-MS) m/z: Calcd for $C_{12}H_{10}N_2S$ $[M + H]^+$ 215.2862 found: 215.2868.

(3n): 3-(benzo[*b*]thiophen-3-yl)-8-fluoro-1-isobutylimidazo[1,5-*a*]pyridine

Oily compound; yield: 152mg (76%); ^{1}H NMR (400 MHz DMSO-d_6): δ 8,32 (s, 1H), 8.26–8.22 (m, 1H), 8.16 (d, *J* = 6.8 Hz, 1H), 8.09–8.05 (m, 1H), 7.47–7.42 (m, 2H), 6.63–6.54 (m, 2H), 2.83 (d, *J* = 6.4 Hz, 2H), 2.10–2.03 (m, 1H), 0.94 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.6, 153.1, 139.6, 137.9, 133.6, 131.77, 131.71, 127.3, 125.5, 125.2, 124.8, 124.4, 123.2, 120.4, 120.0, 119.4, 112.9, 112.8, 101.3, 37.4, 29.7, 22.7; HRMS (ESI-MS) m/z: Calcd for $C_{19}H_{17}FN_2S$ $[M + H]^+$ 325.4151 found: 325.4150.

(3o): 3-(pyridine-4-yl)imidazo[1,5-*a*]pyridine

Pale yellow solid; yield: 166mg (83%); MP 96–98 °C; ^{1}H NMR (400 MHz DMSO-d_6): δ 9.08 (s, 1H), 8.67 (d, *J* = 4.0 Hz, 1H), 8.25 (d, *J* = 7.2 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.60–7.44 (m, 1H), 6.80–6.76 (m, 1H), 6.65 (t, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.3, 148.4, 135.2, 132.1, 126.8, 123.7, 121.45, 121.41, 120.9, 113.7; HRMS (ESI-MS) m/z: Calcd for $C_{12}H_9N_3$ $[M + H]^+$ 195.2200 found: 195.2201.

(3p): 3-isopropylimidazo[1,5-*a*]pyridine

Oily Compound; yield: 134mg (67%); ^{1}H NMR (400 MHz DMSO-d_6): δ 7.75 (d, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 9.2 Hz 1H), 6.65–6.61(m, 1H), 6.53 (t, *J* = 6.4 Hz 1H), 3.35–3.28 (m, 1H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.4, 130.3, 120.4, 118.7, 117.4, 111.9, 26.0, 20.4; HRMS (ESI-MS) m/z: Calcd for $C_{10}H_{12}N_2$ $[M + H]^+$ 160.2157 found: 160 2154.

(3q): 3-(tert-butyl)imidazo[1,5-*a*]pyridine

Oily Compound; yield: 138mg (69%); ^{1}H NMR (400 MHz DMSO-d_6): δ 8.34 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 9.6 Hz, 1H), 7.22 (s, 1H), 6.70–6.65 (m, 1H), 6.58 (t, *J* = 6.8 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.0, 131.6, 123.8, 118.9, 117.89, 117.83, 112.0, 28.2, 27.4; HRMS (ESI-MS) m/z: Calcd for $C_{11}H_{14}N_2$ $[M + H]^+$ 174.2423 found: 174.2427.

(5a): 3-Phenyl-[1,2,4]triazolo[4,3-*a*]pyridine

Pale brown solid; yield: 178mg (89%); MP 172–174 °C; ^{1}H NMR (400 MHz DMSO-d_6) δ 9.08 (s, 1H), 8.66 (d, *J* = 3.2 Hz, 1H), 8.24 (d, *J* = 7.4 Hz, 1H), 8.13 (d, *J* = 8 Hz, 1H), 7.54 (s, 1H), 7.51-7.47 (m, 1H), 7.45 (t, *J* = 5.6 Hz, 1H), 6.80-6.67 (m, 1H), 6.63 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.5, 146.7, 130.1, 129.2, 128.2, 126.9, 126.6, 122.6, 116.8, 114.1; HRMS (ESI-MS) m/z: Calcd for $C_{12}H_9N_3$ $[M + H]^+$ 195.0796 found: 195.0793.

(5b): 3-(p-tolyl)-[1,2,4]triazolo[4,3-*a*]pyridine

Pale yellow solid; yield: 170mg (85%); MP 118–120 °C; ^{1}H NMR (400 MHz DMSO-d_6): δ 8.19 (t, *J* = 6.8 Hz, 1H), 7.70 (t, *J* = 9.2 Hz, 1H), 7.64-7.60 (m, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.20-7.18 (m, 1H), 6.78 (t, *J* = 6.4 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.3, 146.7, 140.3, 129.9, 28.0, 126.6, 122.6, 116.6, 116.5, 114.0, 21.4; HRMS (ESI-MS) m/z: Calcd for $C_{13}H_{11}N_3$ $[M + H]^+$ 209.2465 found: 209.2462.

(5c): 3-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-*a*]pyridine

Pale yellow solid; yield: 168mg (84%); MP 121–123 °C; ^{1}H NMR (400 MHz DMSO-d_6): δ 8.20 (d, *J* = 6.8 Hz, 1H), 7.77-7.71 (m, 3H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 8 Hz, 2H), 6.81 (t, *J* = 6.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.0, 129.7, 126.6, 122.5, 118.9, 116.7, 113.9, 55.4; HRMS (ESI-MS) m/z: Calcd for $C_{13}H_{11}N_3O$ $[M + H]^+$ 225.2459 found: 225.2458.

(5d): **3-isopropyl-[1,2,4]triazolo[4,3-*a*]pyridine**

Oily compound; yield: 140mg (70%); ^{1}H NMR (400 MHz DMSO-d_6): δ 7.91 (d, *J* = 7.2 Hz 1H), 7.76 (d, *J* = 9.6 Hz 1H), 7.26–7.19 (m, 1H), 6.84 (t, *J* = 6.4 Hz 1H), 1.53 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 151.0, 149.7, 126.4, 122.0, 116.2, 113.2, 24.9, 20.0; HRMS (ESI-MS) m/z: Calcd for $C_9H_{11}N_3$ $[M + H]^+$ 161.2037 found: 161.2036.

(5e): 3-(pyridine-4-yl)imidazo[1,5-*a*]pyridine

Pale yellow solid; yield: 144mg (72%); MP 125–127 °C; ^{1}H NMR (400 MHz DMSO-d_6): δ 9.08 (s, 1H), 8.67 (d, *J* = 4.0 Hz, 1H), 8.25 (d, *J* = 7.2 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.60–7.44 (m, 1H), 6.80–6.76 (m, 1H), 6.65 (t, *J* = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 149.3, 148.4, 135.2, 132.1, 126.8, 123.7, 121.45, 121.41, 120.9, 113.7; HRMS (ESI-MS) m/z Calcd for $C_{12}H_9N_3$ $[M + H]^+$ 196.2080 found: 196.2079.

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References:

(1) (a) J. Bermudez, C. S. Fake, G. F. Joiner, K. A. Joiner, F. D. King, W. D. Miner and G. J. Sanger, *J. Med. Chem.,* 1990, **33**, 1924; (b) G. Trapani, M. Franco, A. Latrofa, L. Ricciardi, A. Carotti, M. Serra, E. Sanna, G. Biggio and G. Liso, *J. Med. Chem*., 1999, **42**, 3934.

(2) (a) A. Cappelli, G. Giuliani, S. Valenti, M. Anzini, S. Vomero, G. Giorgi, C. Sogliano, E. Maciocco, G. Biggio and A. Concas, *Bioorg and Med. Chem.,* 2004, **16**(6*), 3428*; (b) T. S. Harrison, G. M. Keating and *CNS Drugs*. 2005, **19**, 65; (c) K. Mizushige, T. Ueda, K. Yukiiri and H. Suzuki, *Cardiovasc. Drugs. Rev*. 2002, **20**(3), 163.

(3) (a) S. Nakano and N. Sugimoto, *Chem. Lett*., 2005, **34**, 1222; (b) H. Nakamura and H. Yamamoto, PCT Int. Appl. WO 2005043630; *Chem. Abstr.,* 2005, **142**, 440277.

(4) (a) J. Gubin, H. de. Vogelaer, H. Inion, C. Houben, J. Lucchetti, J. Mahaux, G. Rosseels, M. Peiren and M. Clinet, *J. Med. Chem.,* 1993, **36**(10), 1425; (b) N. Höfgen, H. Stange, R. Schindler, H. J. Lankau, C. Grunwald, B. Langen, U. Egerland, P. Tremmel, M. N. Pangalos, K. L. Marquis, T. Hage, B. L. Harrison, M. S. Malamas, N. J. Brandon and T. Kronbach, *J. Med. Chem*., 2010, **53**(11), 4399; (c) S. C. Goodacre, L. J. Street, D. J. Hallett, J. M. Crawforth, S. Kelly, A. P. Owens, W. P. Blackaby, R. T. Lewis, J. Stanley, A. J. Smith, P. Ferris, B. Sohal, S. M. Cook, A. Pike, N. Brown, K. A. Wafford, G. Marshall, J. L. Castro and J. R. Atack, *J. Med. Chem*., 2006, **49**, 35.

(5) (a) K. F. McClure , Y. A. Abramov, E. R. Laird, J. T. Barberia, W. Cai, T. J. Carty, S. R. Cortina, D. E. Danley, A. J. Dipesa, K. M. Donahue, M. A. Dombroski, N. C. Elliott, C. A. Gabel, S. Han, T. R.Hynes, P. K. LeMotte, M. N. Mansour, E. S. Marr, M. A. Letavic, J. Pandit, D. B. Ripin, F. J. Sweeney, D. Tan and Y. Tao, *J. Med. Chem*., 2005, **48**, 5728; (b) D. Kim, L. Wang, J. J. Hale, C. L. Lynch, R. J. Buddu, M. MacCoss, S. G. Mills, L. Malkowitz, S. L. Gould, J. A. DeMartino, M. S. Springer, D. Hazuda, M. Miller, J. Kessler, R. C. Hrin, G. Carver, A. Carella, K. Henry, J. Lineberger, W. A. Schleif and E. A. Emini, *Bioorg.& Med. Chem. Lett*., 2005, **15**, 2129; (c) A. K. Sadana, Y. Mirza, K. R. Aneja, O. Prakash, *Eu. J. Med. Chem.,* 2003, **38**(5), 533; (d) S. Sarges, H. R. Howard, R. G. Browne, L. A. Label, L. P. A. Seymour and B. K. Koe, *J. Med. Chem*., 1990, **33**, 2240.

(6) (a) G. R. Pettit, J. C. Collins, J. C. Knight, D. L. Herald, R. A. Nieman, M. D. Williams and R. K. Pettit, *J. Nat. Prod*., 2003, **66**,

544; (b) M. Mohamed, T. P. Goncalves, R. J. Whitby, H. F. Sneddon and D. C. Harrowven, *A. Chem. Eur. J*., 2011, **17**, 13698; (c) D. Knueppel and S. F. Martin, *Angew. Chem., Int. Ed.,* 2009, **48**, 2569; (d) M. D. Markey and T. R. Kelly. *J. Org. Chem*., 2008, **73**, 7441.

(7) (a) S. W. Schneller and D. G. Bartholomew, *J. Het. Chem.,* 1978, **15**, 439; (b) H. Reimlinger and W. R. F. Lingier, *Chem. Ber.,* 1975, **108**, 3787.

(8) (a) A. Moulina, J.Martineza and J. A. Fehrentz, *Tett. Lett.,* 2006, **47**, 7591; (b) J. Y. Roberge, G. Yu, A. Mikkilineni, X. Wu, Y. Zhu, R. M. Lawrence and W. R. Ewing, *ARKIVOC,* 2007; (xii), **132**; (c) A. Reichelt, J. R. Falsey, R. M. Rzasa, O. R. Thiel, M. M. Achmatowicz, R. D. Larsen and D. Zhang, *Org. Lett.,* 2010, **12**(4), 792.

(9) G. Pelletier and A. B. Charette. *Org. Lett.,* 2013, **15**(9), 2290.

(10) J. J. Li, A. K. Trehan, H. S. Wong, S. Krishnananthan, L. J. Kennedy, Q. Gao, J. A. Robl, B. Balasubramanian and B. C. Chen, *Org. Lett*., 2008**, 10**, 2897.

(11) J. M. Crawforth and M. Paoletti, *Tetrahedron. Lett.,* 2009, **50**(34), 4916.

(12) M. A. Schmidt and X. Qian, *Tetrahedron. Lett.,* 2013, **54**(42), 5721.

(13) K. S. Vadagaonkar, K. Murugan, A. C. Chaskar and P. M. Bhate. *RSC Adv*., 2014, **4**, 34056

(14) (a) B. Prabhu, T. M. Vishwanatha, N. R. Panguluri and V. V. Sureshbabu, *Synthesis*., 2013, **45**(12), 1569; (b) H. Wissmann and H. J. Kleiner, *Angew. Chem., Int. Ed.,* 1980, **92**, 133; (c) K. M. Sharnabai, G. Nagendra, T. M. Vishwanatha and V. V. Sureshbabu, *Tetrahedron. Lett.,* 2013, **54**(6), *478*; (d) A. Meudt, S. Scherer and S. Nerdinger, PCT Int. Appl. WO 2005070879, *Chem. Abstr*., 2005, **143**, 172649; (e) W. Holla, B. Napierski and H. P. Rebenstock, Ger. Offen. DE 19802969, 1999; *Chem. Abstr*., 1999, **131**, 131507; (f) J. K. Augustine, R. Kumar, A. Bombrun and A. B. Mandal, *Tetrahedron. Lett.,* 2011, **52**(10), 1074; (g) B. Vasantha, H. P. Hemantha and V. V. Sureshbabu, *Synthesis*., 2010, **17**, 2990; (h) S. Poojari, P. P. Naik and G. Krishnamurthy, *Tetrahedron. Lett*., 2012, **53**(35), 4639; (i) J. K. Augustine, V. Vairaperumanl, S. Narasimhan, P. Alagarsamy, and A. Radhakrishnan. *Tetrahedron.,* 2009, **65**, 9989; (j) M. Jida and B. Deprez. *New J. Chem.,* 2012, **36**, 869; (k) S. Hermann, Ger. Offen. DE 10063493, 2002; *Chem. Abstr.,* 2002, **137**, 47003.

(15) (a) G. M. Raghavendra, A. B. Ramesha, C. N. Revanna, K. N. Nandeesh, K. Mantelingu and K. S. Rangappa, *Tetrahedron.Lett*., 2011**, 52**, 5571; (b) A. B. Ramesha, G. M. Raghavendra, K. N. Nandeesh, K. S. Rangappa and K. Mantelingu*, Tetrahedron. Lett*., 2013, **54**, 95; (c) K. S. Sharath Kumar, T. R. Swaroop, K. B. Harsha, K. H. Narasimhamurthy and K. S. Rangappa, *Tetrahedorn. Lett.,* 2012, **53**(42), 5619.

(16) (a) S. Vijay Kumar, S. K. Yadav, B. Raghava, B. Saraiah, H. Ila, K. S. Rangappa, A. Hazra, *J. Org. Chem.,* 2013, **78**(10), 4960; (b) T. A. Jenifer Vijay, K. N. Nandeesh, G. M. Raghavendra, K. S. Rangappa and K. Mantelingu, *Tetrahedron. Lett*., 2013, **54**, 6533; (c) G. S. Lingaraju, T. R. Swaroop, A. C. Vinayaka, K. S. Sharath Kumar, M. P. Sadashiva and K. S. Rangappa, *Synthesis.,* 2012, **44**(9), 1373; (d) A. C. Vinayaka, M. P. Sadashiva, X. Wu, S. S. Biryukov, J. A. Stoute, K. S. Rangappa and D. Channe Gowda, *Org. Biomol. Chem*., 2014, **12**, 8555; (e) B. Raghava, G. Parameshwarappa, A. Acharya, T. R. Swaroop, K. S. Rangappa and H. Ila, *Eu. J. Org. Chem.,* 2014, **9**, 1882.

(17) C. S. Pavan Kumar, K. B. Harsha, N. C. Sandhya, A. B. Ramesha, K. Mantelingu and K. S. Rangappa, *New J. Chem.,* 2015, **39**, 8397.

(18) C. S. Pavan Kumar, K. B. Harsha, K. Mantelingu and K. S. Rangappa, *RSC Adv*., 2015, **5**, 61664.

(19) K. Mantelingu, Y. Lin and D.Seidel, *Org. Lett*., 2014, **16**(22),5910.

(20) J. K. Augustine, A. Bombrun, W. H. B. Sauer and P. Vijaykumar, *Tetrahedron. Lett*., 2012, **53**, 5030.

(21) J. K. Augustine, A. Bombrun and S. Venkatachaliah, *Tetrahedron. Lett*., 2011, **52**, 6814.

Novel Approach for the Synthesis of Imidazo and Triazolopyridines from Dithioesters

Ajjahalli. B. Ramesha,[a] Nagarakere. C. Sandhya,[b] Chottanahalli. S. Pavan Kumar,[a] Mahanthawamy Hiremath,[a] Kempegowda Mantelingu[a]* and Kanchugarakoppal. S. Rangappa,[a]*

Various Imidazo and Triazolopyridines were synthesised by the intramolecular cyclization of pyridine 2-methylamine and dithioesters under mild conditions.